Saizen®

[somatropin (rDNA origin) for injection]

For subcutaneous or intramuscular injection

DESCRIPTION

Saizen® [somatropin (rDNA origin) for injection] is a human growth hormone produced by recombinant DNA technology. Saizen® has 191 amino acid residues and a molecular weight of 22,125 daltons. Its amino acid sequence and structure are identical to the dominant form of human pituitary growth hormone. Saizen® is produced by a mammalian cell line (mouse C127) that has been modified by the addition of the human growth hormone gene. Saizen®, with the correct three-dimensional configuration, is secreted directly through the cell membrane into the cell-culture medium for collection and purification.

Saizen® is a highly purified preparation. Biological potency is determined by measuring the increase in body weight induced in hypophysectomized rats.

Saizen® is a sterile, non-pyrogenic, white, lyophilized powder intended for subcutaneous or intramuscular injection after reconstitution with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol). The reconstituted solution has a pH of 6.5 to 8.5.

Saizen® is available in 5 mg and 8.8 mg vials. The quantitative composition per vial is:

5 mg vial:

Each vial contains 5 mg somatropin, 34.2 mg sucrose and 1.16 mg O-phosphoric acid. The pH is adjusted with sodium hydroxide or O-phosphoric acid.

8.8 mg vial:

Each vial contains 8.8 mg somatropin, 60.2 mg sucrose and 2.05 mg O-phosphoric acid. The pH is adjusted with sodium hydroxide or O-phosphoric acid.

The diluent is Bacteriostatic Water for Injection, USP containing 0.9% Benzyl Alcohol added as an antimicrobial preservative.

Saizen® is also available in the click.easy® reconstitution device. The quantitative composition per vial contained in the click.easy® reconstitution device is:

8.8 mg vial contained in the click.easy® device:

Each vial contains 8.8 mg somatropin, 60.2 mg sucrose and 2.05 mg O-phosphoric acid. The pH is adjusted with sodium hydroxide or O-phosphoric acid.

4 mg vial contained in the click.easy® device:

Each vial contains 4 mg somatropin, 27.3 mg sucrose and 0.9 mg O-phosphoric acid. The pH is adjusted with sodium hydroxide or O-phosphoric acid.

The diluent in the click.easy® device contains 0.3% (w/v) metacresol in Sterile Water for Injection added as an antimicrobial preservative. The reconstituted solution has a pH of 6.5 to 8.5.

CLINICAL PHARMACOLOGY

General

In vitro, preclinical, and clinical testing have demonstrated that Saizen® [somatropin (rDNA origin) for injection] is therapeutically equivalent to pituitary-derived human growth hormone. Clinical studies in normal adults also demonstrated equivalent pharmacokinetics.

Actions that have been demonstrated for Saizen®, somatrem, and/or pituitary-derived human growth hormone include:

A. Tissue Growth-

   1. Skeletal Growth: Saizen® stimulates skeletal growth in prepubertal children with pituitary growth hormone deficiency. Skeletal growth is accomplished at the epiphyseal plates at the ends of long bone. Growth and metabolism of epiphyseal plate cells are directly stimulated by growth hormone and one of its mediators, insulin-like growth factor-I. Serum levels of insulin-like growth factor-I (IGF-I) are low in children and adolescents who are growth hormone deficient, but increase during treatment with Saizen®. Linear growth continues until the growth plates fuse at the end of puberty.
   2. Cell Growth: Treatment with pituitary-derived human growth hormone results in an increase in both the number and the size of skeletal muscle cells.
   3. Organ Growth: Growth hormone of human pituitary origin influences the size and function of internal organs and increases red cell mass. Saizen® has been shown to promote similar organ weight increase to pituitary human growth hormone in an adequate animal model.

B. Protein Metabolism-Linear growth is facilitated in part by growth hormone-stimulated protein synthesis. This is reflected by increased cellular uptake of amino acids and nitrogen retention as demonstrated by a decline in urinary nitrogen excretion and blood urea nitrogen during growth hormone therapy.

C. Carbohydrate Metabolism-Growth hormone is a modulator of carbohydrate metabolism. Children with inadequate secretion of growth hormone sometimes experience fasting hypoglycemia that is improved by treatment with growth hormone. Saizen® therapy may decrease glucose tolerance. Administration of Saizen® to normal adults and patients with growth hormone deficiency resulted in transient increases in mean serum fasting and postprandial insulin levels. However, glucose levels remained in the normal range.

D. Lipid Metabolism-Acute administration of human growth hormone to humans results in lipid mobilization. Nonesterified fatty acids increase in plasma within one hour of Saizen® administration. In growth hormone deficient patients, long-term growth hormone administration often decreases body fat. Mean cholesterol levels decreased in patients treated with Saizen®. The clinical significance of this is unknown.

E. Mineral Metabolism- Growth hormone administration results in the retention of total body potassium, phosphorus, and sodium. Serum calcium levels appear to be unaffected.

F. Connective Tissue/Bone Metabolism-Growth hormone stimulates the synthesis of chondroitin sulfate and collagen as well as the urinary excretion of hydroxyproline.

Pharmacokinetics

Absorption - The absolute bioavailability of recombinant human growth hormone (r-hGH) after subcutaneous administration ranges between 70-90%.

Distribution - The mean volume of distribution of r-hGH given to healthy volunteers was estimated to be 12.0 ± 1.08 L.

Metabolism - The metabolic fate of somatropin involves classical protein catabolism in both the liver and kidneys. In renal cells, at least a portion of the breakdown products is returned to the systemic circulation. The mean half-life of intravenous somatropin in normal males is 0.6 hours, whereas subcutaneously and intramuscularly administered somatropin has a half-life of 1.75 and 3.4 hours, respectively. The longer half-life observed after subcutaneous or intramuscular administration is due to slow absorption from the injection site.

Excretion - The mean clearance of intravenously administered r-hGH in six normal male volunteers was 14.6 ± 2.8 L/hr.

Special Populations

Pediatric - The pharmacokinetics of r-hGH is similar in children and adults.

Gender - No gender studies have been performed in children. In adults, the clearance of r-hGH in both men and women tends to be similar.

Race - No data are available.

Renal Insufficiency - Children and adults with chronic renal failure tend to have decreased clearance of r-hGH as compared to normals.

Hepatic Insufficiency - A reduction in r-hGH clearance has been noted in patients with hepatic dysfunction as compared with normal controls.

CLINICAL STUDIES

ADULT GROWTH HORMONE DEFICIENCY (GHD)

A multicenter, randomized, double-blind, placebo-controlled clinical trial was conducted in 115 adults with GHD comparing the effects of Saizen® [somatropin (rDNA origin) for injection] and placebo on body composition. Patients in the active treatment arm were treated with Saizen® at an initial dose of 0.005 mg/kg/day for one month which was increased to 0.01 mg/kg/day if tolerated for the remaining five months of the study. The primary endpoint was the change from baseline in lean body mass (LBM) measured by dual energy X-ray absorptiometry (DXA) after 6 months. Treatment with Saizen® produced significant ($p<0.001$) increases from baseline in LBM compared to placebo (Table 1).

Table 1 – Lean Body Mass (kg) by DXA

	Saizen® (n=52)	Placebo (n=51)
Baseline (mean)	47.7	54.0
Change from baseline at 6 months (mean)	+1.9	-0.2
Treatment difference (mean) 95% confidence interval p-value	2.1 (1.3, 2.9) <0.001	

Sixty-seven (58%) of the 115 randomized patients were male. The adjusted mean treatment difference on the increase in LBM from baseline was significantly greater in males (2.9 kg) than females (0.8 kg).

Ninety-seven (84%) of the 115 randomized patients had adult onset (AO) GHD. The adjusted mean treatment differences on the increase in LBM from baseline were not significantly different in AO GHD (2.1 kg) compared with childhood onset (CO) GHD (1.0 kg) patients. However, there were relatively few patients with CO GHD (n=18) on which to base the comparison.

Analysis of the treatment difference on the change from baseline in total fat mass (by DXA) revealed a significant decrease ($p<0.001$) in the Saizen®-treated group compared to the placebo group. Saizen® also produced beneficial effects on several bone turnover markers including bone specific alkaline phosphatase, c-terminal propeptide, osteocalcin, urine deoxypyridinoline and iPTH.

One hundred and eleven patients were enrolled in an open label follow up study and treated with Saizen® for an additional 6-30 months. During this period, the beneficial effects on LBM and total fat mass achieved during the initial six months of treatment were maintained.

INDICATIONS AND USAGE

Pediatric Patients

Saizen® [somatropin (rDNA origin) for injection] is indicated for the long-term treatment of children with growth failure due to inadequate secretion of endogenous growth hormone.

Adult Patients

Saizen® [somatropin (rDNA origin) for injection] is indicated for replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria:

Adult Onset: Patients who have growth hormone deficiency, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or

Childhood Onset: Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

In general, confirmation of the diagnosis of adult growth hormone deficiency in both groups usually requires an appropriate growth hormone stimulation test. However, confirmatory growth

hormone stimulation testing may not be required in patients with congenital/genetic growth hormone deficiency or multiple pituitary hormone deficiencies due to organic disease.

CONTRAINDICATIONS

Saizen® is contraindicated in patients with a known hypersensitivity to somatropin or any of its excipients.

Saizen® reconstituted with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol) should not be administered to patients with a known sensitivity to Benzyl Alcohol (see WARNINGS).

Somatropin should not be used for growth promotion in pediatric patients with closed epiphyses.

Somatropin is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy.

In general, somatropin is contraindicated in the presence of active malignancy. Any pre-existing malignancy should be inactive and its treatment complete prior to instituting therapy with somatropin. Somatropin should be discontinued if there is evidence of recurrent activity. Since growth hormone deficiency may be an early sign of the presence of a pituitary tumor (or, rarely, other brain tumors), the presence of such tumors should be ruled out prior to initiation of treatment. Somatropin should not be used in patients with any evidence of progression or recurrence of an underlying intracranial tumor.

Somatropin should not be used to treat patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions in intensive care units revealed a significant increase in mortality (41.9% vs. 19.3%) among somatropin-treated patients (doses 5.3-8 mg/day) compared to those receiving placebo (see WARNINGS).

Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (see WARNINGS). Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, Saizen® is not indicated for the long term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

WARNINGS

There have been reports of fatalities after initiating therapy with somatropin in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnea, or unidentified respiratory infection. Male patients with one or more of these factors may be at greater risk than females. Patients with Prader-Willi syndrome should be evaluated for signs of upper airway obstruction and sleep apnea before initiation of treatment with somatropin. If, during treatment with somatropin, patients show signs of upper airway obstruction (including onset of or increased snoring) and/or new onset sleep apnea, treatment should be interrupted. All patients with Prader-Willi syndrome treated with somatropin should also have effective weight control and be monitored for signs of respiratory infection, which should be diagnosed as early as possible and treated aggressively

(see CONTRAINDICATIONS). Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, Saizen® is not indicated for the long term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

Benzyl Alcohol as a preservative in Bacteriostatic Water for Injection, USP has been associated with toxicity in newborns. If sensitivity to the diluent occurs, Saizen® [somatropin (rDNA origin) for injection] may be reconstituted with Sterile Water for Injection, USP. When Saizen® is reconstituted in this manner, the reconstituted solution should be used immediately and any unused solution should be discarded.

See CONTRAINDICATIONS for information on increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure. The safety of continuing somatropin treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with somatropin in patients having acute critical illnesses should be weighed against the potential risk.

PRECAUTIONS

General:

Saizen® [somatropin (rDNA origin) for injection] therapy should be carried out under the regular guidance of a physician who is experienced in the diagnosis and management of pediatric patients with growth hormone deficiency or adult patients with either childhood-onset or adult-onset growth hormone deficiency.

Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses in susceptible patients. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during somatropin treatment. Therefore, glucose levels should be monitored periodically in all patients treated with somatropin, especially in those with risk factors for diabetes mellitus, such as obesity (including obese patients with Prader-Willi syndrome), Turner syndrome, or a family history of diabetes mellitus. Patients with preexisting type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored closely during somatropin therapy. The doses of antihyperglycemic drugs (i.e., insulin or oral agents) may require adjustment when somatropin therapy is instituted in these patients.

Patients with preexisting tumors or growth hormone deficiency secondary to an intracranial lesion should be examined routinely for progression or recurrence of the underlying disease process. In pediatric patients, clinical literature has revealed no relationship between somatropin replacement therapy and central nervous system (CNS) tumor recurrence or new extracranial tumors. However, in childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with somatropin after their first neoplasm. Intracranial tumors, in particular meningiomas, in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in a small number of patients treated with somatropin products. Symptoms usually occurred within the first eight (8) weeks after the initiation of somatropin

therapy. In all reported cases, IH-associated signs and symptoms rapidly resolved after cessation of therapy or a reduction of the somatropin dose. Funduscopic examination should be performed routinely before initiating treatment with somatropin to exclude preexisting papilledema, and periodically during the course of somatropin therapy. If papilledema is observed by funduscopy during somatropin treatment, treatment should be stopped. If somatropin-induced IH is diagnosed, treatment with somatropin can be restarted at a lower dose after IH-associated signs and symptoms have resolved. Patients with Turner syndrome, chronic renal insufficiency, and Prader-Willi syndrome may be at increased risk for the development of IH.

In patients with hypopituitarism (multiple hormone deficiencies), standard hormonal replacement therapy should be monitored closely when somatropin therapy is administered.

Undiagnosed/untreated hypothyroidism may prevent an optimal response to somatropin, in particular, the growth response in children. Patients with Turner syndrome have an inherently increased risk of developing autoimmune thyroid disease and primary hypothyroidism. In patients with growth hormone deficiency, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment. Therefore, patients treated with somatropin should have periodic thyroid function tests and thyroid hormone replacement therapy should be initiated or appropriately adjusted when indicated.

Patients should be monitored carefully for any malignant transformation of skin lesions.

When somatropin is administered subcutaneously at the same site over a long period of time, tissue atrophy may result. This can be avoided by rotating the injection site.

As for any protein, local or systemic allergic reactions may occur. Parents/Patient should be informed that such reactions are possible and that prompt medical attention should be sought if allergic reactions occur.

Pediatric Patients (see PRECAUTIONS, General):

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders (including pediatric growth hormone deficiency and Turner syndrome) or in patients undergoing rapid growth. Any pediatric patient with the onset of a limp or complaints of hip or knee pain during somatropin therapy should be carefully evaluated.

Progression of scoliosis can occur in patients who experience rapid growth. Because somatropin increases growth rate, patients with a history of scoliosis who are treated with somatropin should be monitored for progression of scoliosis. However, somatropin has not been shown to increase the occurrence of scoliosis. Skeletal abnormalities including scoliosis are commonly seen in untreated Turner syndrome patients. Scoliosis is also commonly seen in untreated patients with Prader-Willi syndrome. Physicians should be alert to these abnormalities, which may manifest during somatropin therapy.

Adult Patients (see PRECAUTIONS, General):

Patients with epiphyseal closure who were treated with somatropin replacement therapy in childhood should be reevaluated according to the criteria in INDICATIONS AND USAGE before continuation of somatropin therapy at the reduced dose level recommended for growth hormone deficient adults. Fluid retention during somatropin replacement therapy in adults may occur. Clinical manifestations of fluid retention are usually transient and dose dependent (see ADVERSE REACTIONS).

Experience with prolonged treatment in adults is limited.

Information for Patients:

Patients being treated with Saizen® (and/or their parents) should be informed about the potential benefits and risks associated with Saizen® treatment. This information is intended to better educate patients (and caregivers); it is not a disclosure of all possible adverse or intended effects.

Patients and caregivers who will administer Saizen® should receive appropriate training and instruction on the proper use of Saizen® from the physician or other suitably qualified health care professional. A puncture-resistant container for the disposal of used syringes and needles should be strongly recommended. Patients and/or parents should be thoroughly instructed in the importance of proper disposal, and cautioned against any reuse of needles and syringes. This information is intended to aid in the safe and effective administration of the medication.

Laboratory Tests:

Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone (PTH), and IGF I may increase with somatropin therapy.

Drug Interactions:

Somatropin inhibits 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) in adipose/hepatic tissue and may significantly impact the metabolism of cortisol and cortisone. As a consequence, in patients treated with somatropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked requiring glucocorticoid replacement therapy. In addition, patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses; this may be especially true for patients treated with cortisone acetate and prednisone since conversion of these drugs to their biologically active metabolites is dependent on the activity of the 11βHSD-1 enzyme.

Excessive glucocorticoid therapy may attenuate the growth promoting effects of somatropin in children. Therefore, glucocorticoid replacement therapy should be carefully adjusted in children with concomitant GH and glucocorticoid deficiency to avoid both hypoadrenalism and an inhibitory effect on growth.

There was no evidence in the controlled studies of an interaction between Saizen® and any of the drugs commonly used in the treatment of routine pediatric problems/illnesses.

Limited published data indicate that somatropin treatment increases cytochrome P450 (CP450) mediated antipyrine clearance in man. These data suggest that somatropin administration may alter the clearance of compounds known to be metabolized by CP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine). Careful monitoring is advisable when somatropin is administered in combination with other drugs known to be metabolized by CP450 liver enzymes. However, formal drug interaction studies have not been conducted.

In adult women on oral estrogen replacement, a larger dose of somatropin may be required to achieve the defined treatment goal (see DOSAGE AND ADMINISTRATION).

In patients with diabetes mellitus requiring drug therapy, the dose of insulin and/or oral agent may require adjustment when somatropin therapy is initiated (see PRECAUTIONS, *General*).

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long-term animal studies for carcinogenicity have not been performed with Saizen®. There is no evidence from animal studies to date of Saizen®-induced mutagenicity or impairment of fertility.

Pregnancy:

Teratogenic Effects: Pregnancy Category B. Reproduction studies have been performed in rats and rabbits at doses up to 31 and 62 times, respectively, the human (child) weekly dose based on body surface area. The results have revealed no evidence of impaired fertility or harm to the fetus due to Saizen®. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Women:

It is not known whether Saizen® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Saizen® is administered to a nursing woman.

Geriatric Use:

The safety and effectiveness of Saizen® in patients aged 65 and over has not been evaluated in clinical studies. Elderly patients may be more sensitive to the action of Saizen®, and therefore may be more prone to develop adverse reactions. A lower starting dose and smaller dose increments should be considered for older patients (see DOSING AND ADMINISTRATION).

ADVERSE REACTIONS

Growth Hormone Deficient Pediatric Patients

As with all protein pharmaceuticals, a small percentage of patients may develop antibodies to the protein. Anti-growth hormone (GH) antibody capacities below 2 mg/L have not been associated with growth attenuation. In some cases when binding capacity exceeds 2 mg/L, growth attenuation has been described. In clinical studies with Saizen® involving 280 patients (204 naive and 76 transfer patients), one patient at 6 months of therapy developed anti-GH antibodies with binding capacities exceeding 2 mg/L. Despite the high binding capacity, these antibodies were not growth attenuating. The patient was subsequently shown to have a hGH-N gene defect. Thus, genetic analysis should be undertaken in any patient in whom anti-GH antibodies with high binding capacities occur. No antibodies against proteins of the host cells were detected in the sera of patients treated up to five years.

Any patient with well-documented growth hormone deficiency who fails to respond to therapy should be tested for antibodies to human growth hormone and for thyroid status.

In clinical studies in which Saizen® was administered to growth hormone deficient children, the following events were infrequently seen: local reactions at the injection site (such as pain, numbness, redness and swelling), hypothyroidism, hypoglycemia, seizures, exacerbation of preexisting psoriasis and disturbances in fluid balance.

Leukemia has been reported in a small number of growth hormone deficient patients treated with growth hormone. It is uncertain whether this increased risk is related to the pathology of growth hormone deficiency itself, growth hormone therapy, or other associated treatments such as

radiation therapy for intracranial tumors. So far, epidemiological data fail to confirm the hypothesis of a relationship between growth hormone therapy and leukemia.

Growth Hormone Deficient Adult Patients

During the 6 month placebo-controlled study, adverse events were reported in 56 patients (93.3%) in the somatropin-treated group and 42 patients (76.4%) in the placebo-treated group. Adverse events with an incidence of ≥5% in Saizen®-treated patients which were more frequent in Saizen®-treated patients compared with placebo-treated patients are listed in Table 2. Arthralgia, myalgia, peripheral edema, other types of edema, carpal tunnel syndrome, paraesthesia and hypoaesthesia were common in the somatropin-treated patients and reported more frequently than in the placebo group. These types of adverse events are thought to be related to the fluid accumulating effects of somatropin. During the placebo-controlled portion of the study, approximately 10% of patients without preexisting diabetes mellitus or impaired glucose tolerance treated with somatropin manifested mild, but persistent, abnormalities of glucose tolerance, compared with none in the placebo group. During the open label phase of the study, approximately 10% of patients treated with somatropin required a small upward adjustment of thyroid hormone replacement therapy for preexisting central hypothyroidism and 1 patient was newly diagnosed with central hypothyroidism. In addition, during the open label phase of the study, when all patients were being treated with somatropin, two patients with preexisting central hypoadrenalism required upward titration of hydrocortisone maintenance therapy which was considered to be suboptimal (unrelated to intercurrent stress, surgery or disease), and 1 patient was diagnosed *de novo* with central adrenal insufficiency after six months of somatropin treatment. Anti-GH antibodies were not detected.

Table 2 Adverse Events with ≥5% Overall Incidence in Saizen®-Treated Patients Which Were More Frequent in Saizen®-Treated Patients Compared with Placebo-Treated Patients During a 6 Month Study

Adverse Event	Saizen-Treated (N=60)	Placebo (N=55)
Arthralgia	14(23.3%)	7(12.7%)
Headache	11(18.3%)	8(14.5%)
Influenza-like symptoms	9(15%)	3(5.5%)
Edema peripheral	9(15%)	2(3.7)
Back pain	6(10%)	5(9.1%)
Myalgia	5(8.3%)	2(3.6%)
Rhinitis	5(8.3%)	2(3.6%)
Dizziness	4(6.7%)	3(5.5%)
Upper respiratory tract infection	4(6.7%)	2(3.6%)
Paraesthesia	4(6.7%)	1(1.8%)
Hypoaesthesia	4(6.7%)	0
Edema dependent	3(5%)	2(3.6%)
Nausea	3(5%)	2(3.6%)
Skeletal Pain	3(5%)	1(1.8%)
Carpal tunnel syndrome	3(5%)	1(1.8%)

Edema generalized	3(5%)	0
Chest pain	3(5%)	0
Depression	3(5%)	0
Hypothyroidism	3(5%)	0
Insomnia	3(5%)	0

N = number of patients

The adverse event pattern observed during the open label phase of the study was similar to the one presented above.

OVERDOSAGE

Short-term overdosage could lead initially to hypoglycemia and subsequently to hyperglycemia. Moreover, overdose with somatropin is likely to cause fluid retention.

Long-term overdosage could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess human growth hormone.

DOSAGE AND ADMINISTRATION

Pediatric Growth Hormone Deficiency (GHD)

Saizen® [somatropin (rDNA origin) for injection] dosage and schedule of administration should be individualized for each patient. The recommended weekly dosage is 0.18 mg/kg of body weight. It should be divided into equal doses given either on 3 alternate days, 6 times per week or daily. The subcutaneous route of administration is preferable; intramuscular injection is also acceptable.

Treatment with Saizen® of growth failure due to growth hormone deficiency should be discontinued when the epiphyses are fused. Patients who fail to respond adequately while on Saizen® therapy should be evaluated to determine the cause of unresponsiveness.

Adult Growth Hormone Deficiency (GHD)

Based on the weight-based dosing utilized in the original pivotal study described herein, the recommended dosage at the start of therapy is not more than 0.005 mg/kg given as a daily subcutaneous injection. The dosage may be increased to not more than 0.01 mg/kg/day after 4 weeks according to individual patient requirements. Clinical response, side effects, and determination of age-and gender-adjusted serum IGF-I levels may be used as guidance in dose titration.

Alternatively, taking into account more recent literature, a starting dose of approximately 0.2 mg/day (range, 0.15-0.3 mg/day) may be used without consideration of body weight. This dose can be increased gradually every 1-2 months by increments of approximately 0.1-0.2 mg/day, according to individual patient requirements based on the clinical response and serum IGF-I concentrations. During therapy, the dose should be decreased if required by the occurrence of adverse events and/or serum IGF-I levels above the age- and gender-specific normal range. Maintenance dosages vary considerably from person to person.

A lower starting dose and smaller dose increments should be considered for older patients, who are more prone to the adverse effects of somatropin than younger individuals. In addition, obese individuals are more likely to manifest adverse effects when treated with a weight-based regimen. In order to reach the defined treatment goal, estrogen-replete women may need higher doses than men. Oral estrogen administration may increase the dose requirements in women.

Drug Preparation Instructions-Vials

To prevent possible contamination, wipe the rubber vial stopper with an antiseptic solution before puncturing it with the needle. It is recommended that Saizen® be administered using sterile, disposable syringes and needles. The syringes should be of small enough volume that the prescribed dose can be drawn from the vial with reasonable accuracy.

After determining the appropriate patient dose, reconstitute each vial of Saizen® as follows: 5 mg vial with 1-3 mL of Bacteriostatic Water for Injection, USP (Benzyl Alcohol preserved); 8.8 mg vial with 2-3 mL of Bacteriostatic Water for Injection, USP (Benzyl Alcohol preserved). Approximately 10% mechanical loss can be associated with reconstitution and multidose administration. For use in patients sensitive to the diluent, see "WARNINGS."

To reconstitute Saizen®, inject the diluent into the vial of Saizen® aiming the liquid against the glass vial wall. Swirl the vial with a GENTLE rotary motion until contents are dissolved completely. DO NOT SHAKE. Because Saizen® growth hormone is a protein, shaking can result in a cloudy solution. The Saizen® solution should be clear immediately after reconstitution. DO NOT INJECT Saizen® if the reconstituted product is cloudy immediately after reconstitution or refrigeration. Occasionally, after refrigeration, small colorless particles may be present in the Saizen® solution. This is not unusual for proteins like Saizen®.

Drug Preparation Instructions-click.easy® cartridges

For drug preparation instructions for Saizen® click.easy® cartridges, please refer to the instructions for use provided with the click.easy® reconstitution device.

STABILITY AND STORAGE

Before Reconstitution - Saizen® [somatropin (rDNA origin) for injection] should be stored at room temperature (15°-30°C/59°-86°F). Expiration dates are stated on the labels.

After Reconstitution - Saizen® 5 mg and 8.8 mg vials reconstituted with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol) provided should be stored under refrigeration (2°-8°C/36°-46°F) for up to 14 days.

Saizen® click.easy® cartridges reconstituted with the diluent containing 0.3% (w/v) metacresol in Sterile Water for Injection should be stored under refrigeration (2°-8°C/36°-46°F) for up to 21 days.

Avoid freezing reconstituted vials or cartridges of Saizen®.

HOW SUPPLIED

Saizen can be administered using (1) a standard sterile, disposable syringe and needle, (2) a compatible Saizen® needle-free injection device or (3) compatible Saizen® needle injection device. For proper use, refer to the Instructions for Use provided with the administration device.

Saizen® [somatropin (rDNA origin) for injection] is a sterile, non-pyrogenic, white, lyophilized powder supplied in packages containing:

1 vial of 5 mg Saizen® and 1 vial of 10 mL Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol) NDC 44087-1005-2

1 vial of 8.8 mg Saizen® and 1 vial of 10 mL Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol) NDC 44087-1088-1

1 click.easy® cartridge of 4 mg (1.5 mg/mL) Saizen® and 2.66 mL diluent containing 0.3% (w/v) metacresol in Sterile Water for Injection NDC 44087-0015-1

5 click.easy® cartridges of 4 mg (1.5 mg/mL) Saizen® and 2.66 mL diluent containing 0.3% (w/v) metacresol in Sterile Water for Injection NDC 44087-0015-5

1 click.easy® cartridge of 8.8 mg (5.83 mg/mL) Saizen® and 1.51 mL diluent containing 0.3% (w/v) metacresol in Sterile Water for Injection NDC 44087-1080-1

5 click.easy® cartridges of 8.8mg (5.83 mg/mL) Saizen® and 1.51 mL diluent containing 0.3% (w/v) metacresol in Sterile Water for Injection NDC 44087-1080-2

1 click.easy® cartridge of 8.8 mg (8 mg/mL) Saizen® and 1.10 mL diluent containing 0.3% (w/v) metacresol in Sterile Water for Injection NDC 44087-2080-1

5 click.easy® cartridges of 8.8 mg (8 mg/mL) Saizen® and 1.10 mL diluent containing 0.3% (w/v) metacresol in Sterile Water for injection NDC 44087-2080-5

Rx Only

October 2007

Manufactured for: EMD Serono, Inc., Rockland, MA 02370 USA

® - Registered trademark of EMD Serono, Inc., Rockland, MA 02370

- -tear off- -

click.easy Reconstitution Device

Saizen®

[somatropin (rDNA origin) for injection]

INSTRUCTIONS FOR USE

For complete dosing and safety information, please refer to the Saizen® [somatropin (rDNA origin) for injection] Package Insert.

COMPOSITION

Each vial of Saizen® 8.8 mg contained in the **8.0 mg/mL click.easy®** device contains the following ingredients:

- Active substance: Somatropin (Recombinant Human Growth Hormone) 8.8 mg.
- Excipients: Sucrose, Phosphoric acid, Sodium Hydroxide; 1 mL of the reconstituted Saizen® solution contains 8.0 mg of somatropin when reconstituted with the contents of the diluent cartridge.

Each vial of Saizen® 8.8 mg contained in the **5.83 mg/mL click.easy**® device contains the following ingredients:

- Active substance: Somatropin (Recombinant Human Growth Hormone) 8.8 mg.
- Excipients: Sucrose, Phosphoric acid, Sodium Hydroxide; 1 ml of the reconstituted Saizen solution contains 5.83 mg of somatropin when reconstituted with the contents of the diluent cartridge.

Each vial of Saizen® 4 mg contained in the **1.5 mg/mL click.easy®** device contains the following ingredients:

- Active substance: Somatropin (Recombinant Human Growth Hormone) 4 mg.
- Excipients: Sucrose, Phosphoric acid, Sodium Hydroxide; 1 mL of the reconstituted Saizen® solution contains 1.5 mg of somatropin when reconstituted with the contents of the diluent cartridge.

COMPOSITION OF DILUENT

Each cartridge of diluent contained in the click.easy® reconstitution device contains the following ingredients:

8.0 mg/mL click.easy®

- Active substance: Metacresol USP (3.27 mg)
- Excipients: Phosphoric acid 85% to adjust pH, Water for Injection, USP (1.10 mL)

5.83 mg/mL click.easy®

- Active substance: Metacresol USP (4.52 mg)

- Excipients: Phosphoric acid 85% to adjust pH, Water for Injection USP (1.51 mL)

1.5 mg/mL click.easy®

- Active substance: Metacresol USP (7.91 mg)
- Excipients: Phosphoric acid 85% to adjust pH, Water for Injection, USP (2.66 mL)

Patients with a known sensitivity to any of the above active substances or excipients should avoid using this product.

PHARMACEUTICAL FORM

Powder and diluent for solution for injection: Powder and diluent (0.3% (w/v) metacresol in water for injection) for parenteral use.

METHOD AND ROUTE OF ADMINISTRATION

The product (powder in vials) must be reconstituted with the enclosed diluent (0.3% (w/v) metacresol in water for injection) using the click.easy® reconstitution device.

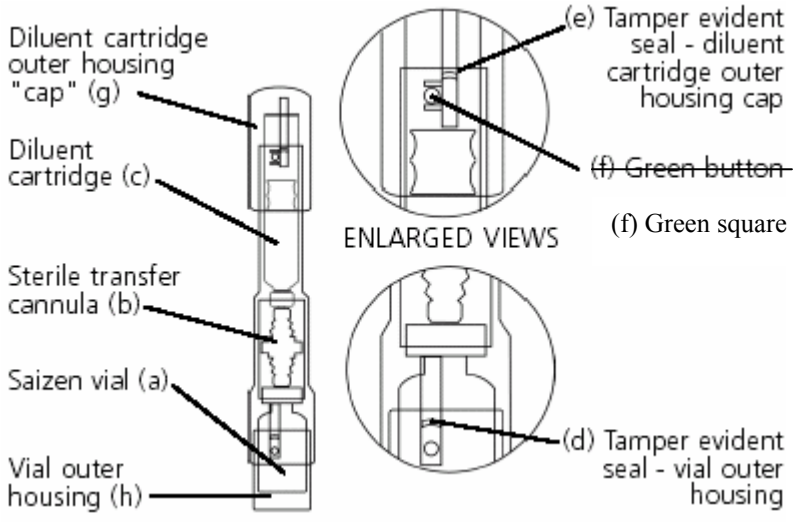
The reconstituted solution is intended for subcutaneous administration (under the skin) and should be clear with no particles. If the solution contains particles, it must not be injected.

IMPORTANT INFORMATION

Patients should be thoroughly instructed in the reconstitution procedure.

For young children, the reconstitution process should be supervised by an adult.

For administration of Saizen® contained in the click.easy® device, please read the following instruction carefully. Please consult your doctor or nurse or pharmacist if you have any questions concerning the reconstitution process.



- Check that the click.easy® reconstitution device contains an unused Saizen® vial (a)and an unused diluent cartridge (c).
- Do NOT use the device if the vial or cartridge appears to be empty or used and return it to your pharmacist or doctor.
- Wash your hands with soap and water.

HOW TO PREPARE YOUR SOLUTION OF SAIZEN®

1. Place the click.easy® device vertically on a flat surface with the Saizen® vial on the bottom and the diluent cartridge outer housing cap (g) on top facing upward.

2. Push on the top diluent cartridge outer housing cap (g) firmly until the Saizen® vial outer housing (h) is completely inside the main body. (This step breaks the tamper evident seal on the vial.

3. Turn the diluent cartridge outer housing cap (g) clockwise until the green square (f) is visible at the lower end of the narrow rectangular opening. Push the diluent cartridge outer housing cap down very slowly until it will go no further and the green colored square appears at the upper end of the narrow rectangular opening.

Check that all the diluent has been transferred into the vial. Dissolve the Saizen® powder with the diluent by gently swirling the click.easy® device (Note: Do not transfer the diluent forcefully or shake the click.easy device. A fast transfer of the diluent or shaking of the click.easy device will create more foam). Let the solution stand for 2-5 minutes until the Saizen® powder is completely dissolved.

4. Turn the click.easy® device upside down so the Saizen® vial is now on top and pull the diluent cartridge outer housing cap slowly downwards until the solution is completely drawn back into the cartridge. Check that no more than one or two drops of solution remain in the vial.

5. If there are more than one or two drops of solution remaining in the vial, slowly push the diluent cartridge outer housing cap up until some of the solution is back in the vial and gently tap the click.easy® device. Then draw the solution slowly again back into the cartridge.

6. Remove any excess air that has been drawn into the cartridge by pushing slowly the cap up until no air bubble is visible in the cartridge. There should be no air bubble in the cartridge. (Note: Avoid pulling the cap down too fast, as this will draw air into the cartridge).

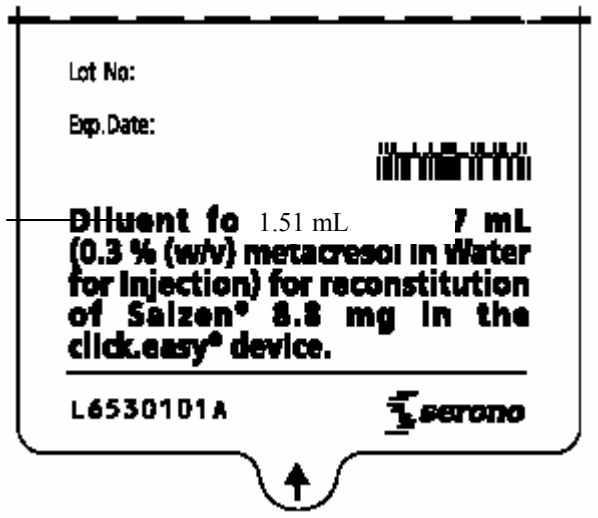
7. Turn the click.easy® device so that the cap is again on the top. Unscrew the cap and remove it.

8. Remove the cartridge containing the reconstituted Saizen® solution from the click.easy® device by grasping the end of the cartridge and pulling straight out of the outer housing.

9.Carefully peel off the outer white label on the cartridge using the tab provided by slowly pulling in the direction of the black arrow.

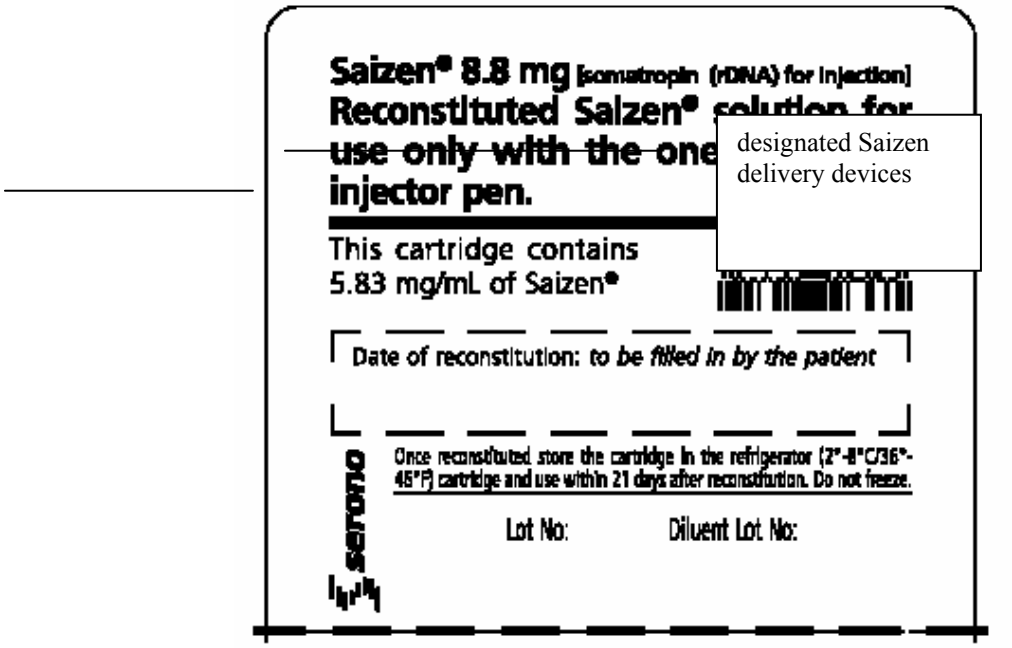
Sample Label

L6530101C



10.Write the reconstitution date on the transparent inner label on the cartridge. This cartridge now contains the reconstituted Saizen® solution that will be used for your treatment.

Sample Label



11.The cartridge containing the reconstituted Saizen® solution is now ready to be used (Note: Please read the instruction manual provided with the injection device for instruction on how to inject the reconstituted Saizen® solution from the cartridge).

12.The Saizen® reconstituted solution should be stored in a refrigerator (2°-8°C / 36°-46°F) and should be used within 21 days after reconstitution. Do not freeze.

13.Discard the click.easy® device containing the empty Saizen® vial safely in accordance with your local requirements. It is not necessary to remove the empty Saizen® vial from the click.easy® device prior to disposal.

Injections should be given in different parts of your body. Do not use any areas in which you feel lumps, firm knots, depressions, or pain; talk to your doctor or healthcare professional about anything you find. Clean the skin at the injection site with soap and water.

STABILITY AND STORAGE

Vials of Saizen® pre-assembled in the click.easy® reconstitution device should be stored in the original package at room temperature (15°-30°C / 59°-86°F).

Saizen® reconstituted solution should be stored in a refrigerator (2°-8°C / 36°-46°F) and should be used within 21 days after reconstitution.

Do not freeze.

HOW SUPPLIED

Saizen® contained in the click.easy® device is available in the following pack sizes:

- 1 vial of Saizen® 8.8 mg product and 1 cartridge of 1.10 mL diluent pre-assembled in 1 reconstitution device (click.easy®) comprising 1 device housing and 1 sterile transfer cannula NDC 44087-1089-1
- 5 vials of Saizen® 8.8 mg product and 5 cartridges of 1.10 mL diluent pre-assembled in 5 reconstitution devices (click.easy®) comprising each 1 device housing and 1 sterile transfer cannula NDC 44087-1089-2
- 1 vial of Saizen® 8.8 mg product and 1 cartridge of 1.51 mL diluent pre-assembled in 1 reconstitution device (click.easy®) comprising 1 device housing and 1 sterile transfer cannula. NDC 44087-xxxx-x
- 5 vials of Saizen® 8.8 mg product and 5 cartridges of 1.51 mL diluent pre-assembled in 5 reconstitution devices (click.easy®) comprising each 1 device housing and 1 sterile transfer cannula. NDC 44087-xxxx-x
- 1 vial of Saizen® 4 mg product and 1 cartridge of 2.66 mL diluent pre-assembled in 1 reconstitution device (click.easy®) comprising 1 device housing and 1 sterile transfer cannula NDC 44087-xxxx-x
- 5 vials of Saizen® 4 mg product and 5 cartridges of 2.66 mL diluent pre-assembled in 5 reconstitution devices (click.easy®) comprising each 1 device housing and 1 sterile transfer cannula NDC 44087-xxxx-x

Manufactured for:

EMD Serono Inc., Rockland, MA 02370

Rx Only BX Rated

October 2007

Need help?
Call connections for growth®
800-582-7989

easypod™

Instructions For Use

saizen®
[somatropin (rDNA origin) for injection]

saizen®
[somatropin (rDNA origin) for injection]

Quick Contacts

For replacement needles
Call Connections for Growth®.....800-582-7989

If easypod™ does not work properly
Call Connections for Growth.....800-582-7989

Default Settings Table

Your easypod comes programmed with the following default settings.
These settings may be changed to suit your individual preference.

Note: Clinical settings should only be changed under the guidance of your healthcare provider.

Comfort settings	Default
Needle speed	Medium
Injection speed	Medium
Injection depth	6 mm
Injection time	5 seconds

Device settings	Default
Date & Time	day/month/year
Sound	On
Name	easypod
Welcome picture	easypod
Language	English

Clinical settings	Default
Dose settings	
Daily dose	0.15 mg
Weight	1 kg
Height	1 cm
Posology (Pos)	0.025 mg/kg/day or 0.7 mg/m²/day
Frequency	7 days/week
Dose adjustment	Off
Cartridge	B (5.83 mg/mL)
Needle type	29 G x 12 mm
Cartridge expiration	28 days
Dose log	On
PIN code	0000

EMD SERONO

Table of Contents

A Message about easypod™ to Saizen® [somatropin (rDNA origin) for injection] Patients and their Caregivers

- easypod is a smart injector, which means it automatically inserts a needle and delivers a preset dose of Saizen®. Your easypod is a personal device; for use by one person only.
- easypod should only be used according to this instruction manual and only after proper training from a healthcare provider. For children, an adult should supervise the use of easypod.

  The "Teach me" section (see page 24) may be used to review the formal training you received.
- easypod is to be used exclusively with Saizen click.easy® cartridges, in accordance with the prescription written by your healthcare provider. Prior to delivery with easypod, Saizen must be reconstituted (mixed) using click.easy. Be sure to write the date of reconstitution on the transparent inner label on the click.easy cartridge. easypod is not designed for use with any other cartridges.

  Detailed information about reconstitution and administration of Saizen is provided in the Saizen Package Insert and the click.easy Instructions for Use.
- easypod is compatible with Saizen click.easy cartridges in the following concentrations: (a) 8 mg/mL; (b) 5.83 mg/mL; and, (c) 1.5 mg/mL. You should check the expiration date printed on the click.easy carton prior to use.
- easypod should be handled with care. When possible, store easypod in the storage case provided, which limits exposure to dirt, dust, liquid, and other substances.

- As needed, clean easypod™ with a damp cloth and mild soap solution.

  Do not use harsh chemicals, cleaning solvents, strong detergents, or alcohol solutions, as these could damage easypod. Remove dirt and dust from your easypod with a soft brush.

  CAUTION: Never rinse or immerse easypod or any of its parts in water.

- easypod contains no harmful components.

- easypod should be replaced after three years of use. A new easypod can be obtained through your healthcare provider, or through Connections for Growth® (CFG), the patient-support program provided by EMD Serono. Call CFG toll-free at 800-582-7989.

- easypod should only be used with Serofine™ single-use disposable sterile needles, 0.33 x 12 mm (29 G x 1/2") or 0.30 x 8 mm (30 G x 5/16"). Call Connections for Growth at 800-582-7989 to refill your supply of needles. Dispose of used needles safely and appropriately as recommended by your healthcare provider. easypod is not designed for use with other needles.

  When a needle is attached, and prior to injection, keep the needle and the base of easypod pointing down.

WARNING:

- **easypod is an electromechanical device and should be handled with care. Do not use easypod if it does not work properly and do not attempt to repair a faulty easypod.**

- **easypod should not be turned on near strong electromagnetic sources like an x-ray machine in a medical facility or a security machine at an airport. Use of easypod near common-household electronic devices should not be a problem.**

Section 1. Getting Started

Getting to know easypod™

Front View

Display (Welcome screen)

Power On/Off (indicated by "⏻" symbol)

Selection Buttons

Back View

Removable Rear Cover (to personalize device)

Side View

Cartridge-Door Button

Cartridge Door

Needle Button

Top View

Injection Button

Base View

Battery Cover

Needle Cavity

Skin Sensor

Section 1. Getting Started

First-time use of easypod™

1. Open the storage case by pushing the sliding-release button to the left **(5a)**.
2. Install four new 'AAA' batteries into easypod by unscrewing the battery cover and placing the batteries as shown inside the cover.
3. Turn on easypod by holding down the power "Φ" button **(5b)** until the Welcome screen appears.
4. You will be prompted to change the date and time using the international-standard settings (day/month/year). Once reset, you may change the date and time settings to US format. See "Date & Time", page 11.
5. The default-language setting is English. If you prefer another language, see "Language", page 13.
6. Saizen® [somatropin (rDNA origin) for injection] click.easy® cartridges have a 21-day expiration after reconstitution (mixing). Follow the directions under "Cartridge expiration", page 23, to change the setting to 21 days. easypod will automatically notify you when the cartridge has been in use for 21 days.
7. Make sure the cartridge setting is correct according to your prescription (see "Cartridge", page 21). Then insert a new click.easy cartridge (see "Insertion of a new cartridge or change of an empty/expired cartridge", page 32).

IMPORTANT INFORMATION:

- **Clinical settings should be changed only under guidance from your healthcare provider.**
- **Do not use the window on the cartridge door to gauge the amount of remaining solution in the cartridge.**

Explanation of easypod symbols

Refer to accompanying documents	*Do not freeze*	*Refrigerate device after use*
Power on/off	*DC*	
Dispose of safely according to your local regulations	*Applied part type B (electrical isolation)*	

Section 1. Getting Started

Dose history and Battery status settings

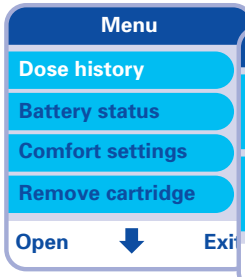
Dose history

1. Select “Menu”. “Dose history” will be highlighted **(6a)**.
2. Select “Open”. “Calendar” will be highlighted.
3. Use the “↓” key to select a display of Dose history in either “Calendar” or “List” format **(6b)**.
4. Select “Open” to see the dose history.
5. Select “Exit” and then “Back” to return to the Menu.
6. Select “Exit” to return to the Welcome screen.

Battery status

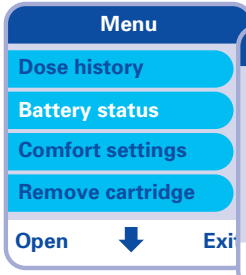
1. Select “Menu”.
2. Use the “↓” key to highlight “Battery status” **(6c)**.
3. Select “Open” to see the battery status.
4. Select “OK” to return to the Menu **(6d)**.
5. Select “Exit” to return to the Welcome screen.

6a

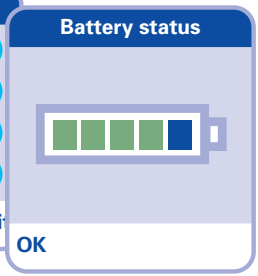


6b

6c



6d



Section 1. Getting Started

Comfort settings

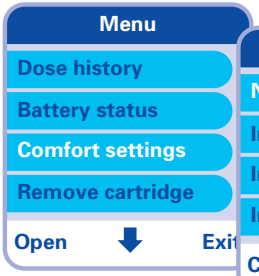
There are four Comfort settings for easypod:

- Needle speed
- Injection speed
- Injection depth
- Injection time

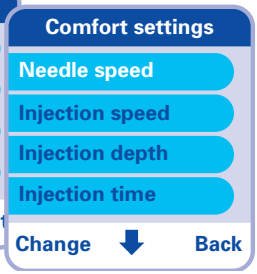
To change a Comfort setting:

1. Select “Menu”.
2. Use the “↓” key to highlight “Comfort settings” **(7a)**.
3. Select “Open”.
4. Follow the instructions on pages 8 and 9 for the Comfort setting you would like to change **(7b)**.
5. Once your setting is changed, select “Back” and then “Exit” to return to the Welcome screen.

7a



7b

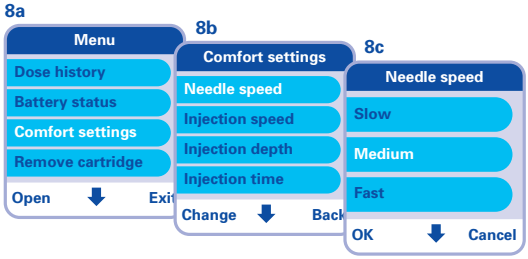


Section 1. Getting Started

Comfort settings

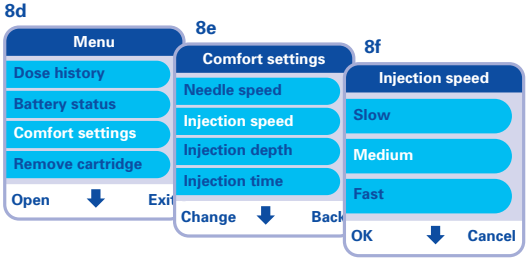
Needle speed – controls how fast the needle is inserted into your skin.

1. Open the "Comfort settings" menu **(8a)**, "Needle speed" will be highlighted.
2. Select "Change" **(8b)** to open the "Needle speed" menu. The current setting will be highlighted.
3. Use the "↓" key to select Slow, Medium, or Fast **(8c)**.
4. Select "OK".



Injection speed – controls how fast your Saizen® [somatropin (rDNA origin) for injection] is delivered.

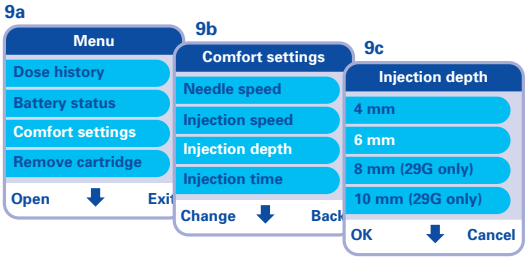
1. Open the "Comfort settings" menu **(8d)**.
2. Use the "↓" key to highlight "Injection Speed" **(8e)**.
3. Select "Change" to open the "Injection speed" menu. The current setting will be highlighted.
4. Use the "↓" key to select Slow, Medium, or Fast **(8f)**.
5. Select "OK".



Comfort settings

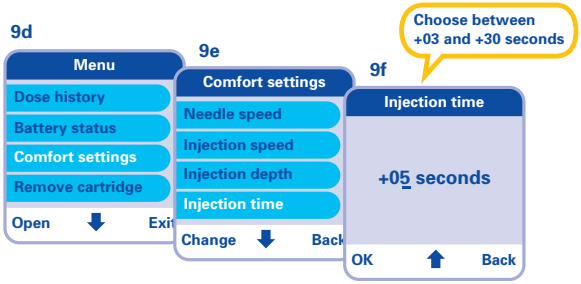
Injection depth – controls how deep the needle is inserted into your skin.

1. Open the "Comfort settings" menu **(9a)**.
2. Use the "↓" key to highlight "Injection depth" **(9b)**.
3. Select "Change" to open the "Injection depth" menu. The current setting will be highlighted.
4. Use the "↓" key to select 4 mm, 6 mm, 8 mm, or 10 mm (8 mm and 10 mm available for 29 G needles only) **(9c)**.
5. Select "OK".



Injection time – controls how long the needle stays in your skin.

1. Open the "Comfort settings" menu **(9d)**.
2. Use the "↓" key to highlight "Injection time" **(9e)**.
3. Select "Change" to open "Injection time". The current setting will be highlighted. Recommended setting is 5 to 10 seconds.
4. Use the "OK" key to move the cursor under the number you would like to change and use the "↑" key to change the number **(9f)**.
5. When the correct number appears, select "OK" to move to the next number.
6. Select "OK".



Section 1. Getting Started

Device settings

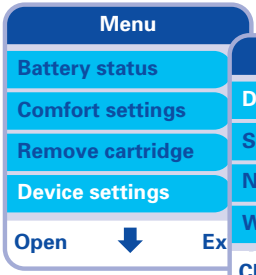
There are five Device settings for easypod:

- Date & Time
- Sound
- Name
- Welcome picture
- Language

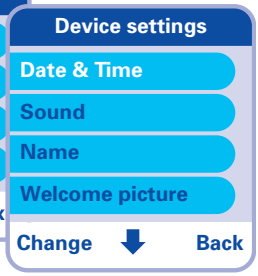
To change a Device setting:

1. Select “Menu”.
2. Use the “↓” key to highlight “Device settings” **(10a)**.
3. Select “Open” to view the Device settings menu.
4. Follow the instructions on pages 11–13 for the Device setting you would like to change **(10b)**.
5. Once your setting is changed, select “Back” and then “Exit” to return to the Welcome screen.

10a



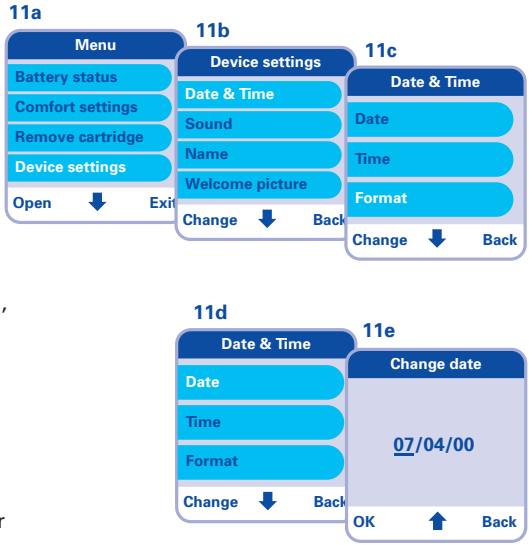
10b



Device settings

Date & Time

1. Open the “Device settings” menu **(11a)**. “Date & Time” will be highlighted.
2. Select “Change” to open the “Date & Time” menu **(11b)**.
3. To change the appearance of the date and time, use the “↓” key to highlight “Format” **(11c)**.
4. Select “Change”.
5. Use the “↓” key to highlight “dd/mm/yy 24h”, “mm/dd/yy am/pm” (US standard format), or “yy/mm/dd 24h”.
6. Select “OK”.
7. To change the date, use the “↓” key to highlight “Date” **(11d)**.
8. Select “Change”.
9. Use the “OK” button to move the cursor under the part of the date you would like to change, and use the “↑” key to change the numbers **(11e)**.



10. When the correct number appears, select “OK” to move to the next number.
11. Continue pressing “OK” until you return to the “Date & Time ” menu.

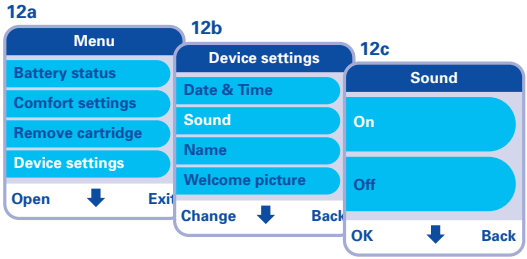
To change the time, use the “↓” key to highlight “Time”. Select “Change”. Use the same steps to change the time as you used to change the date.

Note: Each time the batteries are removed, easypod will prompt you to change the date and time.

Device settings

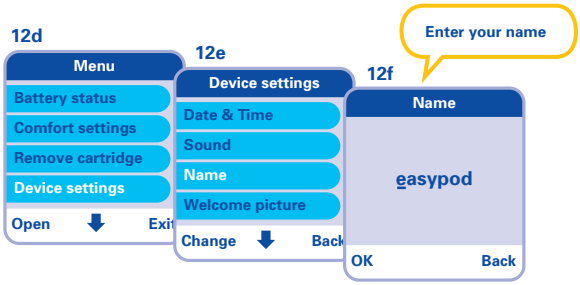
Sound

1. Open the “Device settings” menu (12a).
2. Use the “↓” key to highlight ”Sound” (12b).
3. Select “Change” to open the “Sound” menu. The current setting will be highlighted.
4. Use the “↓” key to choose “On” or “Off” (12c).
5. Select “OK”.



Name

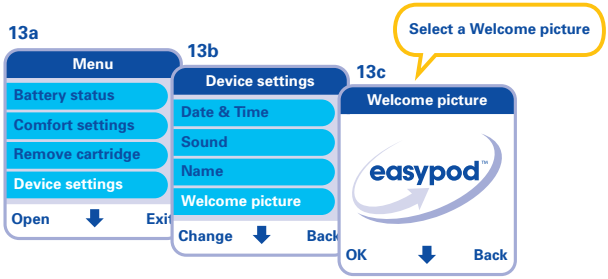
1. Open the “Device settings” menu (12d).
2. Use the “↓” key to highlight “Name” (12e).
3. Select “Change” to open “Name”.
4. Use the “OK” key to move the cursor under the letter you would like to change, and use the “↑” key to scroll through the alphabet (12f).
5. When the correct letter appears, select “OK” to move to the next letter.
6. Continue pressing “OK” until you return to the “Device settings” menu.



Device settings

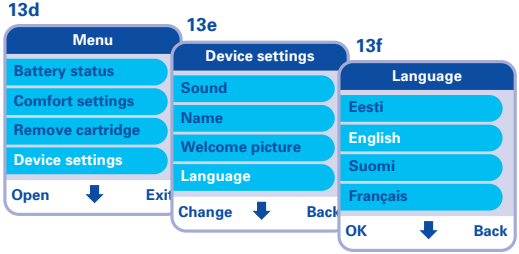
Welcome picture

1. Open the “Device settings” menu **(13a)**.
2. Use the “↓” key to highlight “Welcome picture” **(13b)**.
3. Select “Change” to open “Welcome picture”. The current Welcome picture will appear.
4. Use the “↓” key to scroll through the pictures **(13c)**.
5. Select “OK” when your choice appears.



Language

1. Open the “Device settings” menu **(13d)**.
2. Use the “↓” key to highlight “Language” **(13e)**.
3. Select “Change” to open the “Language” menu. The current setting will be highlighted.
4. Use the “↓” key to scroll through the language options **(13f)**.
5. Select “OK” when your language choice is highlighted.



Section 1. Getting Started

Clinical settings

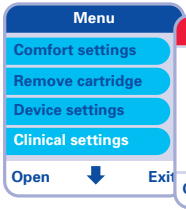
There are six Clinical settings for easypod:

- Dose settings
- Injection settings
- Cartridge expiration
- Dose log
- Connection
- PIN code

To change a Clinical setting:

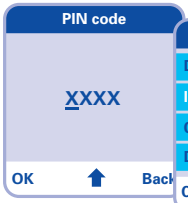
1. Select “Menu”.
2. Use the “↓” key to highlight “Clinical settings” **(14a)**.
3. Select “Open”. The warning message “Changes can affect treatment” will appear **(14b)** and easypod will beep three times.
4. Select “OK” to continue, or “Exit” to return to the Menu. You will be asked for a **PIN code**, which must be entered to change any Clinical setting.
5. Use the “↑” key and then press “OK” to enter the initial PIN code “0000” **(14c)**. The “Clinical settings” menu will open **(14d)**.
6. Follow the instructions on pages 15–23 for the Clinical setting you would like to change.
7. Once your setting is changed, select “Back” and then “Exit” to return to the Welcome screen.

14a

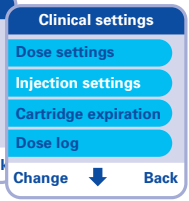


14b

14c



14d



Information about Clinical settings

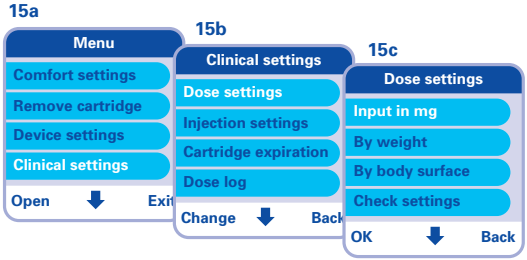
- Clinical settings should be changed only under guidance from your healthcare provider.
- The initial PIN code is “0000” and should be changed only by your healthcare provider.
- “Connection” is not an active feature.

Clinical settings

Dose settings

There are three options in easypod for setting the dose:

- Input in mg
- By weight
- By body surface

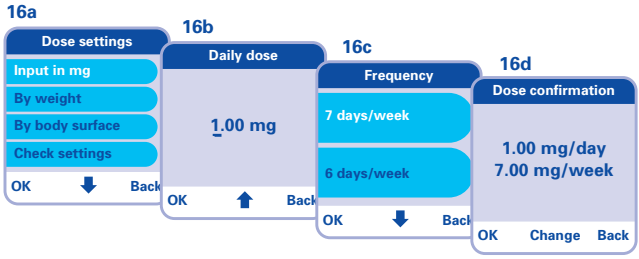


To change a Dose setting:

1. Open the “Clinical settings” menu **(15a)** and enter the PIN code (see page 14). “Dose settings” will be highlighted **(15b)**.
2. Select “Change” to open the “Dose settings” menu.
3. Follow the instructions on pages 16 and 17 to change the dose by mg, weight, or body surface, and for “Check settings” **(15c)**.
4. Follow the instructions on page 18 to use the Dose adjustment feature, which can reduce medication waste.

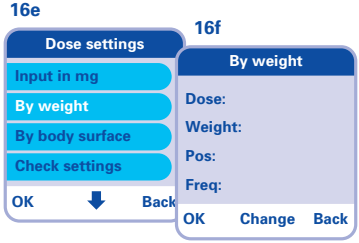
Clinical settings

Input in mg – dose in milligrams



1. Open the "Dose settings" menu **(16a)**. "Input in mg" will be highlighted.
2. Select "OK" to open "Daily dose".
3. Use the "OK" key to move the cursor under any number you would like to change and use the "↑" key to change the number **(16b)**.
4. When the correct number appears, select "OK" to move to the next, until all numbers are correct.
5. Continue pressing "OK" until the "Frequency" menu appears.
6. Use the "↓" key to highlight "7 days/week" or "6 days/week" **(16c)**.
7. Select "OK" and the "Dose confirmation" display will appear.
8. If the dose information is correct, select "OK" **(16d)**, and the "Dose adjustment" menu will appear (see page 18 for instructions). If the dose information is incorrect, select "Change" to return to the "Dose settings" menu and repeat the steps.

By weight – dose per kg of body weight

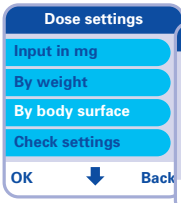


1. Open the "Dose settings" menu and use the "↓" key to highlight "By weight" **(16e)**.
2. Select "OK" to open the "By weight" menu.
3. Select "OK" if the settings are correct, or select "Change" to change the settings **(16f)**.
4. Repeat steps 3 to 8 above (under "Input in mg").

Clinical settings

By body surface – dose per m^2 of body surface

17a



17b

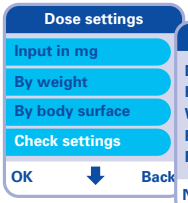
1. Open the "Dose settings" menu and use the "↓" key to highlight "By body surface" (17a).
2. Select "OK" to open the "By body surface" menu.
3. Select "OK" if the settings are correct, or select "Change" to change the settings (17b).
4. Repeat steps 3 to 8 (under "Input in mg", page 16).

Note: Posology ("Pos") on (16f) and (17b) is another term used for "dosing" expressed as mg/kg/day or mg/m^2/day.

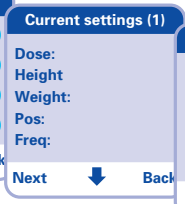
Check settings

This feature allows you to review the Dose settings selected.

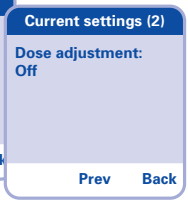
17c



17d



17e



1. Use the "↓" key to highlight "Check settings" from the "Dose settings" menu (17c).
2. Select "OK" to open the "Current settings (1)" menu, showing the current Dose settings.
3. Select "Next" (17d) to open "Current settings (2)", showing the current Dose adjustment setting (17e).
4. Select "Back" to return to the "Dose settings" menu.

Clinical settings

Dose adjustment

The Dose adjustment feature can reduce the amount of medication wasted. There are three settings to choose from: “Off”, “>50%”, and “Automatic”.

To change the Dose adjustment setting:

1. Follow the instructions on pages 16 and 17 to change the dose by mg, weight, or body surface.
2. Select “OK” on the “Dose confirmation” menu **(18a)**, which is step 8 under “Dose settings—Input in mg” (see page 16). The “Dose adjustment” menu will open.
3. Use the “↓” key to highlight “Off”, “>50%”, or “Automatic” **(18b)**.
4. Select “OK”.

5a. WHEN “OFF” IS SELECTED, you will be asked to confirm the daily dose.

If easypod detects that the cartridge content is less than the daily dose, you will be prompted to change the cartridge. Choose **i.** or **ii.** or **iii.** below:

i. inject the full daily dose with a new cartridge; **or,**

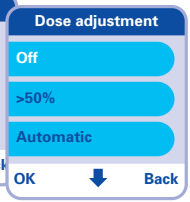
ii. inject the medication remaining in the current cartridge and count this partial dose as the daily dose; **or,**

iii. complete two injections that together total the full daily dose: the first with the remaining medication in the current cartridge; and, the second, with a new cartridge (see “Partial dose”, page 30). easypod will automatically calculate the dose needed for the second injection.

Select “OK”, or “Back” to change the dose settings **(18c)**.

18a

18b



18c

Clinical settings

5b. WHEN ">50%" IS SELECTED, the daily dose, the projected date of the last dose, and the left over medication in the cartridge will be displayed.

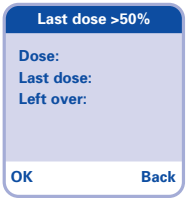
easypod will keep track of the amount of medication remaining in the current cartridge.

i. if >50% (but less than 100%) of the daily dose is remaining in the current cartridge, easypod will inject this partial dose from the current cartridge and record it as the daily dose;

ii. if <50% of the daily dose is remaining in the current cartridge, you will be prompted to change the cartridge and easypod will inject the full daily dose from the new cartridge.

Select "OK", or "Back" to change the dose settings **(19a)**.

19a

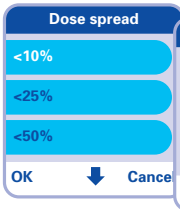


5c. WHEN "AUTOMATIC" IS SELECTED, the "Dose spread" menu will open.

Use the "↓" key to highlight the "Dose spread" setting you want **(19b)**.

easypod will calculate the dose that optimally uses the cartridge content and remains close to the daily dose. The dose will be adjusted by ± 10%, 25% or 50%, whichever is selected on the Dose spread menu.

19b



19c

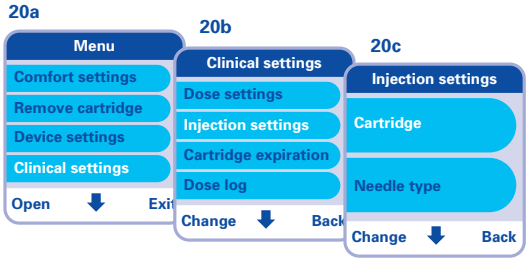
Select "OK" to see the Automatic adjustment and view the min/max daily adjusted dose **(19c)**, or "Cancel" to change the dose settings.

Clinical settings

Injection settings

There are two Injection settings for easypod:

- Cartridge
- Needle type



To change an Injection setting:

1. Open the "Clinical settings" menu **(20a)** and enter the PIN code (see page 14).
2. Use the "↓" key to highlight "Injection settings" **(20b)**.
3. Select "Change" to open the "Injection settings" menu.
4. Follow the instructions on pages 21 and 22 to change an Injection setting **(20c)**.

Section 1. Getting Started

Clinical settings

Cartridge

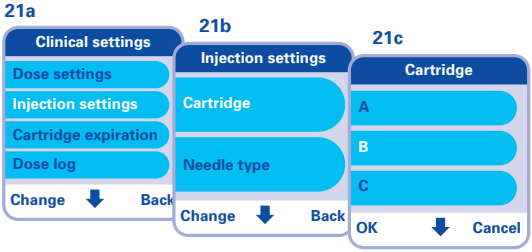
The dose range depends on the type of cartridge selected containing a specified concentration of Saizen® [somatropin (rDNA origin) for injection]. The following click.easy® cartridge concentrations are available:

- Cartridge type A (concentration of 8 mg/mL):
  range can vary between 0.5 mg to 6.4 mg in increments of 0.01 mg.
- Cartridge type B (concentration of 5.83 mg/mL):
  range can vary between 0.15 mg to 4.66 mg in increments of 0.01 mg.
- Cartridge type C (concentration of 1.5 mg/mL):
  range can vary between 0.15 mg to 1.2 mg in increments of 0.01 mg.

IMPORTANT: The cartridge type should be selected according to your prescription.

To change the Cartridge setting:

1. Open the "Clinical settings" menu and enter the PIN code (see page 14) **(21a)**.
2. Use the "↓" key to highlight "Injection settings".
3. Select "Change" to open the "Injection settings" menu. "Cartridge" will be highlighted.
4. Select "Change" and the "Cartridge" menu will open **(21b)**.
5. Use the "↓" key to highlight Cartridge "A", "B", or "C" **(21c)**.
6. Select "OK".



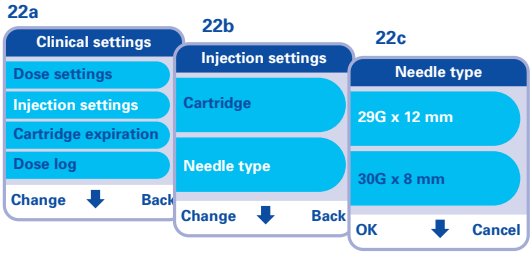
Section 1. Getting Started

Clinical settings

Needle type

easypod should only be used with Serofine™, single-use, disposable sterile needles. Serofine needles are available as a 29 G x 1/2" (12 mm) or a 30 G x 5/16" (8 mm). Choose the appropriate needle type.

To change the Needle type setting:

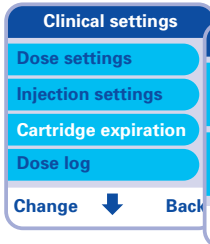


1. Open the "Clinical settings" menu and enter the PIN code (see page 14) **(22a)**.
2. Use the "↓" key to highlight "Injection settings".
3. Select "Change" to open the "Injection settings" menu.
4. Use the "↓" key to highlight "Needle type" **(22b)**, and the "Needle type" menu will open.
5. Use the "↓" key to highlight "29 G" or "30 G" needles **(22c)**.
6. Select "OK".

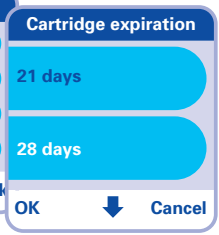
Clinical settings

Cartridge expiration

23a



23b

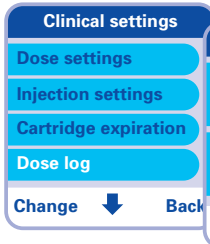


To change the Cartridge expiration setting:

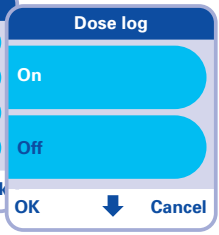
1. Open the "Clinical settings" menu and enter the PIN code (see page 14) (23a).
2. Use the "↓" key to highlight "Cartridge expiration".
3. Select "Change" to open the "Cartridge expiration" menu.
4. Use the "↓" key to highlight "21 days" (23b). (The cartridge expires and must be changed after 21 days).
5. Select "OK".

Dose log

23c



23d



The Dose log keeps track of each dose injected.

To change the "Dose log" setting: Open the "Clinical settings" menu → Open "Dose log" → Activate "Dose log" by highlighting "On" and deactivate by highlighting "Off" → Select "OK".

The Dose history in calendar or list format uses the following color code:

Green = injection completed
Red = injection missed
Orange = partial injection delivered
Black = cartridge changed
Blue = future days

Section 1. Getting Started

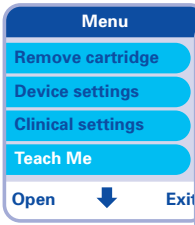
"Teach me"— pictorial demonstration built into easypod™

See the chart below for the easypod operations demonstrated in "Teach me".

To watch "Teach me":

1. Select "Menu" from the Welcome screen.
2. Use the "↓" key to highlight "Teach me" **(24a)**.
3. Select "Open". The first pictorial step will appear **(24b)**.
4. Select "Next" to scroll through each step shown below.

24a



24b

Manual Removal of empty cartridge and insertion of a new cartridge	
Step 1 Attach the Needle	
Step 2 Inject	
Step 3 Detach the needle	
Storage and Needle Disposal	

Section 2. Delivering Saizen® [somatropin (rDNA origin) for injection] with easypod

Preparing for your injection

IMPORTANT: Always start by washing your hands thoroughly with antibacterial soap and water. Make sure to use a clean towel when drying your hands.

1. To turn on easypod, press the power button with the "⏻" symbol and hold down until the Welcome screen appears **(25a)**.

   Note: If your refrigerator is very cold, easypod will be cold. You may want to wait 5 to 10 minutes before turning it on, allowing easypod to adjust to room temperature.

2. Press the Start button. easypod will check the cartridge to determine whether it contains enough medication for your full-dose injection:

   - If the cartridge does not contain enough medication for your full-dose injection, or needs to be manually removed, the display will read "Cartridge empty. Change cartridge" **(25b)**, (see "Partial dose", page 30);
   - If there is enough medication in the cartridge for a full dose, the display will read "Insert new needle".

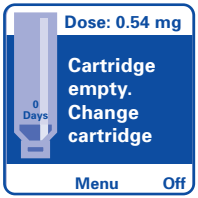
   Note: easypod will display a reminder "Injection completed today. Continue?" if you try to inject within 12 hours of your previous injection **(25c)**. Select "Yes" if you wish to continue.

   Note: easypod will beep every 30 seconds for three minutes if an injection is not completed, and it will turn off automatically after 10 minutes.

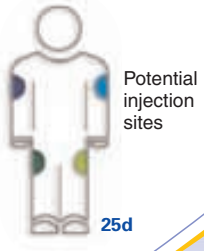
3. Prepare your injection site according to the instructions given by your healthcare provider **(25d)**.

25a

25b



25c



Section 2. Delivering Saizen® [somatropin (rDNA origin) for injection] with easypod

Giving your daily injection in three steps

Step 1: Attach the needle

A. Remove the sterility seal from a new Serofine™ needle cap **(26a)**.

WARNING: Do not use the needle if the sterility seal is damaged or lifting. Make sure to completely remove the sterility seal.

B. Insert the needle cap into the needle cavity on easypod until it locks into place **(26b)**. When inserted correctly, the needle cap clicks into place and easypod will beep once.

IMPORTANT: Do not continue to hold the needle cap while easypod attaches the needle.

When the needle is attached, the display will read "Needle attached Remove empty cap" **(26c)** and easypod will beep twice.

Note: If the needle is not attached correctly, a warning message "Check needle" **(26d)** will be displayed. Follow the prompts to safely detach the needle and replace with a new needle.

C. Remove the needle cap by pushing the cap sideways **(26e)**.

Note: Do not throw the needle cap away. You will need it to detach the used needle after your injection.

26a

26b

26c

26d

26e

Section 2. Delivering Saizen® [somatropin (rDNA origin) for injection] with easypod

Giving your daily injection in three steps

Step 2: Inject

A. When the display reads "Place on skin Press injection button", place easypod at a right angle (90°) against your skin **(27a)**.

When properly positioned against the skin, easypod will beep once and the injection button on top will turn green, indicating you are ready to inject.

IMPORTANT: Do not pinch your skin at the injection site.

B. Press the green injection button once to start your injection **(27b)**. It is not necessary to hold down the injection button.

During injection, the injection button will blink and the display will read "Injection in progress" **(27c)**.

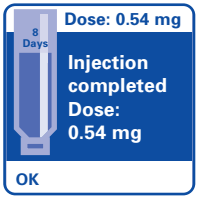
When the injection is complete, the injection-button light will go off and easypod will beep twice.

27a

27b

27c

27d



IMPORTANT: During the injection, hold easypod steady and always in contact with your skin. Removing easypod prior to the end of the injection will result in an incomplete injection.

C. Lift easypod from the skin. The display will read "Injection completed" and show the injected dose **(27d)**. Select "OK" to confirm the injected dose.

Giving your daily injection in three steps

Step 3. Detach the needle

A. When the display reads "Place empty cap", insert the empty needle cap into the needle cavity until it locks into place **(28a)**. easypod will beep once.

IMPORTANT: Make sure you insert an empty cap. Do not continue to hold the needle cap while easypod detaches the needle.

28a

B. When the display reads "Press needle button until beep", press and hold the needle button **(28b)** until easypod beeps twice. The needle is now detached and inside the needle cap.

IMPORTANT: Releasing the needle button too quickly (before the two beeps) may cause the needle to detach incorrectly and a warning message to appear that reads "Check needle is detached". In this case, remove the cap and see if the needle is in the cap. If so, select "OK". If not, place the empty cap back onto easypod, select "Repeat", and follow the prompts.

28b

C. When the needle cap is ready to be removed, the display will read "Remove cap". To remove the used needle and needle cap, push the cap sideways **(28c)**. Dispose of the used needle safely.

IMPORTANT: Remember to dispose of the used needle in a suitable container, as recommended by your healthcare provider.

28c

After your injection

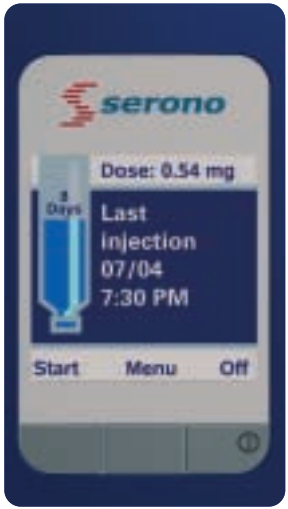
1. When your injection is complete, the Welcome screen will appear and the date and time of your injection will be displayed **(29a)**.
2. To turn off easypod, press and hold the "Power" ("⏻") button until the display is blank.

   Note: Make sure easypod is turned off to preserve the batteries.
3. Place easypod, with the cartridge containing your medication, in its storage case.

   Do not remove the cartridge from easypod unless traveling (see "Manual removal of an in-use cartridge", page 31).
4. Immediately place easypod back into the refrigerator (2-8°C / 36-46°F).

   WARNING: Never store easypod in the freezer.

29a

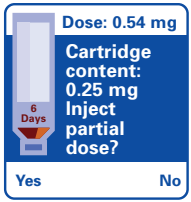


Section 2. Delivering Saizen® [somatropin (rDNA origin) for injection] with easypod

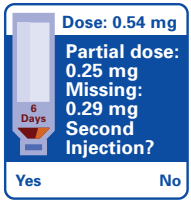
Partial dose

If there is not enough medication in the cartridge for your full dose, the display will read "Inject partial dose?" (30a). Select "Yes" or "No" and follow the instructions below under **A** or **B**, respectively.

30a



30b



A. SELECT "YES" IF YOU WANT A PARTIAL DOSE

Continue your injection of the medication in the current cartridge by following the daily-injection instructions beginning on page 25.

Once the first (partial dose) injection is completed, the display will read "Second injection?" (30b). Select "Yes" or "No" and follow the instructions below under **a** or **b**, respectively.

a. Select "Yes" if you want a second injection, to complete your full dose. Detach the used needle from your first injection by following the instructions on page 28. Change the cartridge as instructed in the section "Insertion of a new cartridge or change of an empty/expired cartridge" on page 32. Follow the daily-injection instructions beginning on page 25.

easypod automatically calculates the dose needed for the second injection and injects this dose.

IMPORTANT: The second injection is automatically canceled if not performed within 60 minutes.

b. Select "No" if you do not want a second injection. The injection procedure is stopped and the display will read "Place empty cap". Follow the instructions to detach the needle on page 28.

B. SELECT "NO" IF YOU DO NOT WANT A PARTIAL DOSE

Follow the instructions for "Insertion of a new cartridge or change of an empty/expired cartridge" on page 32. Once the cartridge is changed, follow the daily-injection instructions beginning on page 25.

Section 3. Maintenance, Care, and Handling of easypod™

A. Traveling with easypod

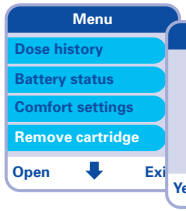
Your cartridge of medication needs to be kept at a temperature between 2-8°C / 36-46°F. If possible, always store it in the refrigerator. If you need to travel with your cartridge of medication, then it should be removed from easypod and stored in an appropriate cooling container (see below "Manual removal of an in-use cartridge").

B. Manual removal of an in-use cartridge (e.g., for traveling)

1. Select "Menu" from the Welcome screen.
2. Use the "↓" key to highlight "Remove cartridge".
3. Select "Open" **(31a)**.
4. easypod will confirm you want the cartridge removed **(31b)**.
   a. If you select "Yes", easypod will beep twice and the message "Open cartridge door" will be displayed.
   b. If you select "No", you will return to the Menu.
5. Open the cartridge door by sliding the cartridge-door button up **(31c)**. easypod will display the message "Insert cartridge" **(31d)**.
6. Remove the cartridge and push closed the cartridge door **(31e)** until a click is heard. The display will read "Continue?".
7. Select "No".
8. Select and hold "Off" until the display is blank to turn off easypod.

Note: When travel is over, see "Insertion of a new cartridge or change of an empty/expired cartridge", page 32, for instructions on reinserting your click.easy® cartridge.

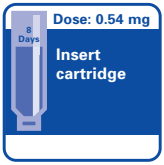
31a



31b

31c

31d



31e

C. Insertion of a new cartridge or change of an empty/expired cartridge

1. If there is no cartridge inside easypod, or no medication left in the cartridge, the display will read "Cartridge empty. Change cartridge" (32a).

   If the cartridge is used for longer than 21 days, the warning "Cartridge expired" will be displayed. The injection-button light will turn red and not allow an injection until the cartridge is replaced.

   Note: easypod has the ability to keep track of the days a cartridge has been in use, starting from the day it is inserted.

   IMPORTANT: easypod must be turned on and the needle detached to change an expired cartridge.

2. Open the cartridge door by sliding the cartridge-door button up (32b). The display will read "Insert cartridge" (32c).

   Note: easypod allows you to open the door only when there is no cartridge inside or it is empty. If the door does not open, the cartridge inside is not empty.

3. If there is an empty or expired cartridge inside easypod, remove it. Then insert a new click.easy® cartridge (32d).

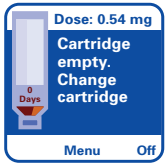
4. Push closed the cartridge door until a click is heard (32e).

5. "Continue?" will be displayed each time a new cartridge is loaded (32f).

6. Select "Yes". easypod will beep once when ready.

   WARNING: To ensure a correct dose, make sure the easypod setting is correct for the cartridge type you are using.

32a



32b

32c

32d

32e

32f

D. Replacing the batteries

The battery-power level is shown by bars changing from green (full), to yellow, to red (low). When the battery-power level is very low, easypod will display the warning "Replace battery" (33a).

33a

You will not be able to inject your next dose until the batteries are changed.

To change the batteries, follow the steps below.

1. Turn off easypod.
2. Use a screwdriver to unscrew the battery cover.
3. Remove the used batteries and appropriately discard them.
4. Insert four new 'AAA' batteries as shown inside the battery cover. **Lithium batteries*** are strongly recommended and expected to last approximately 10 months (supplied with easypod by EMD Serono).
5. Screw the battery cover back onto easypod.
6. Turn on easypod.
7. Reset the date and time. Each time the batteries are changed, the date and time need to be reset (see "Date & Time", page 11).

*Alkaline batteries can be used in easypod and are expected to last approximately six months.

E. Storage

When containing a Saizen® [somatropin (rDNA origin) for injection] click.easy® cartridge, easypod should always be placed in its storage case and stored in the refrigerator (2-8°C / 36-46°F). Before storing, the needle should always be detached.

Section 3. Maintenance, Care, and Handling of easypod™

F. Cleaning easypod

As needed, clean easypod with a damp cloth and mild soap solution. Do not use harsh chemicals, cleaning solvents, strong detergents, or alcohol solutions, as these could damage easypod. Remove dirt and dust with a soft brush.

G. Replacement of easypod

easypod should be replaced after three years of use. A new easypod can be obtained through your healthcare provider or by calling Connections For Growth® (CFG), EMD Serono's patient-support program at 800-582-7989. If you experience problems with your easypod, please contact your health-care provider or CFG. You can record the date you received easypod and its serial number below.

Date Received _____ Serial Number _____

H. Frequently asked questions

IMPORTANT: In case of a problem with easypod, you should contact your healthcare provider or Connections For Growth at 800-582-7989.

What if I cannot turn on easypod?

Leave easypod at room temperature for 5 to 10 minutes. A very-cold refrigerator can affect the performance of the batteries. Try turning easypod on again.

Make sure you are using the correct type of batteries and they are correctly inserted. Lithium batteries are recommended. Try inserting a new set of batteries. To turn on easypod, you need to press and hold the power button ("⏻") until the Welcome screen appears.

H. Frequently asked questions (continued)

What if easypod turns off unexpectedly or if it remains on the same screen?

Check to see if the batteries need to be changed "Menu" → "Battery status". If the problem persists, try new batteries or batteries of a different brand.

What if I cannot attach a needle into easypod?

Make sure you are using Serofine™ needles and that the sterility seal on the needle cap has been completely removed. Try reattaching the needle into your easypod. If you still cannot attach the needle, try a new needle.

What if I remove easypod from my skin during an injection?

If you remove easypod from your skin during an injection (blinking green light on the injection button), the injection will be interrupted and the needle automatically retracted. You can complete the injection within a time period of five minutes and inject the balance of your dose by replacing easypod onto your skin. Or, you can stop the injection, but only a partial dose will have been delivered.

What if I cannot detach a needle from my easypod?

Make sure you have used an empty needle cap to detach the needle. Try detaching the needle again. Make sure to press and hold the needle button until easypod beeps twice. Be careful not to injure yourself when handling the needle and dispose of it safely. If you still cannot detach the needle, you should contact your healthcare provider or CFG by calling 800-582-7989.

H. Frequently asked questions (continued)

What if I lose the empty needle cap?

The empty cap is necessary to detach the used needle safely. If you no longer have an empty cap, you should contact your healthcare provider or Connections For Growth® at 800-582-7989.

What if I start a new injection within 12 hours of my last injection?

If you try to inject within 12 hours of your last injection your easypod will display a reminder "Injection completed today. Continue?" Select "Yes" if you wish to continue with the injection.

What if I drop my easypod?

easypod has a self-checking mechanism to ensure mechanical problems will not lead to dosing errors. If you have dropped easypod and it still turns on, continue use of easypod. In the event of a mechanical problem, easypod will shut down automatically.

What if I drop my easypod and the cartridge breaks?

If a cartridge breaks inside your easypod, you should stop using it immediately. The electronics or mechanics may be damaged by the liquid or pieces of broken glass. Contact your healthcare provider or CFG by calling 800-582-7989, to replace your easypod.

What if I cannot open the cartridge door?

The cartridge door can only be opened when the cartridge is empty and easypod is turned on. If you need to remove an in-use cartridge (e.g., for traveling), see "Manual removal of an in-use cartridge", page 31.

What if the date or time is not correct?

You can change the date or time on easypod. See "Date & Time", page 11.

Section 4. Technical Information about easypod™

Specifications

EMD Serono, Inc.
One Technology Place
Rockland, MA 02370

CE 0086

Model name:	easypod™
Weight:	280g (10.3 oz)
Dimensions:	H: 128mm x W: 66mm x D: 36mm (H: 5in x W: 2.6in x D: 1.4in)
Voltage supply:	6VDC
Supply:	4 x AAA/LR03; 1.5VDC batteries - Energizer Lithium Ultimate (or e2). (Or high-quality alkaline batteries, recommended brands: Varta Power One, Varta High Energy, Varta Maxitech, Philipps PowerLife, Duracell Procell, Duracell Ultra M3).
Battery life:	approx. 10 months with lithium batteries and 6 months with alkaline batteries.
Serial number:	number with 16 digits printed below the bar code on the device label (under the rear cover).
Classification:	MDD 93/42 CEE Class IIa 21 CFR 880.58608 Class II IP20 (easypod not protected against water spillage)
	Applied part type B

Electromagnetic compatibility in accordance with EN60601-1-2 (see EMC tables beginning next page).

Operating environment:	2°C to 30°C (36°F to 86°F), 20%RH to 90%RH, 800hPa to 1060hPa.
Storage condition, (without batteries/cartridge):	-20°C to 60°C (-4°F to 140°F), 20%RH to 75%RH, 800hPa to 1060hPa.
Memory:	All data (except date and time) is stored permanently in easypod.
Cartridge:	Saizen® [somatropin (rDNA origin) for injection] 3mL cartridges.
Maximum injection volume:	0.8mL.
Dose accuracy:	+/-10% for dose above 0.25mL and +/-0.025mL for dose below 0.25mL.
Needles:	Serofine™ needles 0.33x12mm (29 G x ½") or 0.30x8mm (30 G x 5/16").

Opening easypod will void any guarantee.
Repair to be performed only by authorized companies.

Explanation of easypod symbols

Refer to accompanying documents

Power on/off

Dispose of safely according to your local regulations

Do not freeze

DC

Applied part type B (electrical isolation)

Refrigerate device after use

Section 4. Technical Information about easypod™

Electromagnetic Compatibility Tables

Medical electrical equipment needs special precautions regarding EMC (electromagnetic compatibility) and needs to be used according to the EMC information provided below. Portable or mobile RF communications equipment (e.g., mobile phones, pagers...) can affect easypod.

easypod is intended for use in the electromagnetic environment specified below. The user should ensure that easypod is used in such an environment.

Guidance and manufacturer's declaration – electromagnetic emission		
Emissions test	**Compliance**	**Electromagnetic environment – guidance**
RF emissions CISPR 11	Group 1	easypod uses RF energy only for its internal function. Therefore, its RF emissions are very low and not likely to cause interference in nearby electronic equipment.
RF emissions CISPR 11	Class B	easypod is suitable for use in all establishments, including domestic establishments and those directly connected to the public low-voltage power supply network that supplies buildings used for domestic purposes.
Harmonic emissions IEC 61000-3-2	Not applicable	
Voltage fluctuations / flicker emissions IEC 61000-3-3	Not applicable	

Guidance and manufacturer's declaration – electromagnetic immunity			
Immunity test	**IEC 60601 test level**	**Compliance level**	**Electromagnetic environment – guidance**
Electrostatic discharge (ESD) IEC 61000-4-2	± 6 kV contact ± 8 kV air	± 8 kV contact ± 15 kV air	Floors should be wood, concrete or ceramic tile. If floors are covered with synthetic material, the relative humidity should be at least 30%.
Electrostatic transient / burst IEC 61000-4-4	± 2 kV for power supply lines ± 1 kV for input/output lines	Not applicable	Not applicable
Surge IEC 61000-4-5	± 1 kV differential mode ± 2 kV common mode	Not applicable	Not applicable
Voltage dips, short interruptions and voltage variations on power supply input lines IEC 61000-4-11	Not applicable	Not applicable	Not applicable
Power frequency (50/60 Hz)	Not applicable	Not applicable	Not applicable

Electromagnetic Compatibility Tables (continued)

Magnetic field IEC 61000-4-8			
Conducted RF IEC 61000-4-6 Radiated RF IEC 61000-4-3	3 Vrms 150 kHz to 80 MHz 3 V/m 80 MHz to 2,5 GHz	Not applicable 10 V/m 26 MHz to 2,5 GHz	Portable and mobile RF communications equipment should be used no closer to any part of easypod, including cables, than the recommended separation distance calculated from the equation applicable to the frequency of the transmitter. Recommended separation distance: $d = [\frac{3,5}{V_1}]\sqrt{P}$ 150 kHz to 80 MHz $d = [\frac{3,5}{E_1}]\sqrt{P}$ 80 kHz to 800 MHz $d = [\frac{7}{E_1}]\sqrt{P}$ 800 kHz to 2,5 GHz where *P* is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer and *d* is the recommended separation distance in meters (m).[b] Field strengths from fixed RF transmitters, as determined by an electromagnetic site survey[a] should be less than the compliance level in each frequency range.[b] Interference may occur in the vicinity of equipment marked with the following symbol: 
NOTE 1: At 80 MHz and 800 MHz, the separation distance for the higher frequency range applies. NOTE 2: These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.			
a) Field strengths from fixed transmitters, such as base stations for radio (cellular/cordless) telephones and land mobile radios, amateur radio, AM and FM radio broadcast and TV broadcast cannot be predicted theoretically with accuracy. To assess the electromagnetic environment due to fixed RF transmitters, an electromagnetic site survey should be considered. If the measured field strength in the location in which easypod is used exceeds the applicable RF compliance level above, easypod should be observed to verify normal operation. If abnormal performance is observed, additional measures may be necessary, such as reorienting or relocating easypod. b) Over the frequency range 150 kHz to 80 MHz, field strengths should be less than [V1] V/m.			

Recommended separation distances between portable and mobile RF communications equipment and easypod

easypod is intended for use in an electromagnetic environment in which radiated RF disturbances are controlled. The user of easypod can help prevent electromagnetic interference by maintaining a minimum distance between portable and mobile RF communications equipment (transmitters) and easypod as recommended below, according to the maximum output power of the communications equipment.

Rated maximum output of transmitter W	Separation distance according to frequency of transmitter (m)		
	$d = [\frac{3,5}{V_1}]\sqrt{P}$ 150 kHz to 80 MHz	$d = [\frac{3,5}{E_1}]\sqrt{P}$ 80 kHz to 800 MHz	$d = [\frac{7}{E_1}]\sqrt{P}$ 800 kHz to 2,5 GHz
0,01	Not applicable	0,04	0,07
0,1	Not applicable	0,11	0,22
1	Not applicable	0,35	0,7
10	Not applicable	1,11	2,21
100	Not applicable	3,5	7

For transmitters rated at a maximum output power not listed above, the recommended separation distance d in meters (m) can be estimated using the equation applicable to the frequency of the transmitter, where P is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer.

NOTE 1: At 80 MHz and 800 MHz, the separation distance for the higher frequency range applies.

NOTE 2: These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.

This easypod™ Instructions For Use was developed by EMD Serono, Inc., One Technology Place, Rockland, MA 02370.

saizen®
[somatropin (rDNA origin) for injection]

easypod™

Instructions For Use

connections for growth®

Need help?
Call our patient support program at 800-582-7989.

EMD SERONO

PCT-217 Noir
PCT-217 Cyan
PCT-217 Magenta
PCT-217 Jaune
PCT-217 072
PCT-217 Réserve

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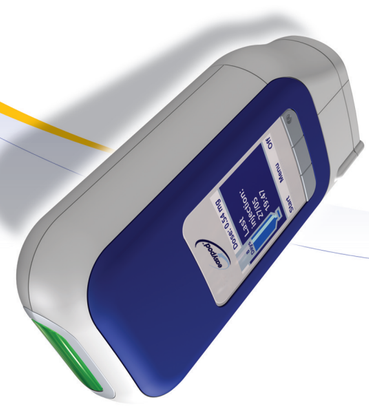

Exclusively for use with
Saizen (somatropin [rDNA]
for injection) click.easy cartridges

Each carton contains:

1 easypod™
for use with Saizen®
(somatropin [rDNA] for
injection) click.easy cartridges

1 storage box

1 instruction manual

4 'AAA' lithium batteries
(included)

Rx only